REMARKS

Applicants request entry of the amendments to the claims under 37 CFR § 1.116(b). The claim amendments (1) comply with requirements of form previously set forth in the final office action and (2) present the claims in better form for consideration on appeal. The amendments to the claims (a) do not raise new issues for consideration and/or search, (b) do not raise the issue of new matter and (c) do not present additional claims without cancelling a corresponding number of finally rejected claims, i.e., two finally rejected claims are cancelled and two new claims replace them. The amendments to the claims reduce and simplify the issues for appeal, e.g., by reducing the scope of claimed compounds in the treatment methods. Therefore, entry of the amendments is appropriate.

The amendments to the claims introduce no new matter. In Applicants prior response to the office action, claims 80-84 were incorrectly numbered as claims 70-74. The claims presented in this paper are numbered in accord with the claim numbering the Office pointed out in the final office action. Exemplary support for the amended claims is summarized below.

Subject matter	support
R^5	-O-C(O)-OCH_3 is at page 39, line 9
R^{17}	-H, -OH and -O-C(O)-CH_3 are at page 39, lines 18, 22 and 27
R^{18}	-OH, -O-C(O)-CH_3 and -O-C(O)-CH_2CH_3 are at page 39, lines 18, 25 and 26
R^{19}	-CCH and -$CCCH_3$ are at page 39, lines 20 and 24

The amendments to the specification add a brief description of figures obtained from Miyamoto et al., *Proc. Natl. Acad. Sci.* USA 96:11173-11177, 1999, of record. The figures and brief description of the figures were in priority application serial No. 60/157,275, filed September 30, 1999, which is incorporated by reference into the present application at page 1. The amendments at pages 79-80 remove the figures from the examples and the examples now refer to the figures. These amendments comply with requirements

of form previously set forth in the final office action and they introduce no new matter. Figures 1-5 accompany this paper.

Rejections under 35 USC § 112, second paragraph

The Office rejected claims 80-81 as allegedly indefinite regarding the definitions of the R^{12} and R^{13} and the R^{16} and R^{17} variable groups, which allegedly were "set forth in the alternative". Applicants do not understand the basis for this objection. However, the amendments to the claims make this ground for rejection moot because the amended claims now recite only R^{17}.

The Office rejected claims 82-83 as indefinite for lacking antecedent basis for R^{18} and R^{19} together being a ketone (=O). The amended claims no longer claim a ketone and dependent claims now have proper antecedent basis for variable group definitions.

In view of the claim amendments, Applicants request reconsideration and withdrawal of the rejections under 35 USC § 112, second paragraph.

Rejections under 35 USC § 112, first paragraph

The Office rejected claims 82-83 as allegedly failing to comply with the written description requirement for lacking support for the R^5 variable "-OC(O)-O-$CH_2)_m$-$(CF_2)_n$-CH_3". Support in the specification for this moiety is at page 36, lines 22-23. However, the amended claims do not recite this variable and this basis for the rejection is now moot.

The Office rejected claims 82-83 as allegedly not enabled because the claims "encompass a very large number of species". Applicants traverse the Office's assertion to the extent it applies to the amended claims. Each of the 4 variable groups in the amended claims recite 1, 2 or 3 specific moieties and no genus. The amended claims therefore recite a very small number of species. Applicants note that the Office's assertion of a lack of enablement is not properly founded and it mistakes a need for data with the teaching of how to make and use the claimed invention. The Application as filed taught how to make and use the claimed subject matter.

Applicants traverse the Office's statement at page 5 that states: "Because there is no way to predict a priori which compounds will be active from the specification or chemical structures alone, an extraordinary amount of trial and error experimentation is required to identify the active compounds." Applicants respectfully submit this statement is not relevant to a proper enablement analysis. The Office has cited no law or case to support the allegation that enablement requires the specification to provide a basis to "predict a priori which compounds will be active". There is no requirement in the Title 35 of the U.S. Code or in any Federal Court holding that imposes a requirement for *a priori* prediction of activity. The Office's comment is therefore irrelevant commentary, which is an insufficient basis to establish a *prima facie* rejection under 35 USC § 112, first paragraph. *In re Marzocchi*, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971).

The scope of enablement of a patent application "is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation." *National Recovery Technologies, Inc. v. Magnetic Separation Systems, Inc.*, 166 F.3d 1190 (Fed. Cir. 1999). In assessing enablement, the court has stated that the number and variety of examples are irrelevant if the disclosure is "enabling" and sets forth the "best mode contemplated." *In re Borkowski*, 422 F.2d 904, 910 (C.C.P.A. 1970). In casting the rejection, Office identified no teaching that was needed to practice the claimed invention. Instead, the Office asserted that "Chang et al show there is great unpredictability in the activities of various of dehydroepiandrosterone". Applicants respectfully disagree with the Office's conclusion and they question its relevance here. Applicants respectfully submit that the Office's assertion of "great unpredictability" in the face of an 18% success rate (4 active compounds out of 22) is simply incorrect. Applicants are aware of no case holding or rule that supports a conclusion of non-enablement in view of these facts and the Office has cited none. The Office points to no teaching that is lacking to enable the

claimed treatment methods. Applicants submit that the application as filed enabled the amended claims.

In view of the claim amendments and foregoing arguments, Applicants request reconsideration and withdrawal of the rejections under 35 USC § 112, first paragraph.

Rejections under 35 USC § 103(a)

The Office rejected claims 80-81 as allegedly obvious over PCT international publication No. WO 97/37662 or Miyamoto et al (*Proc. Natl. Acad. Sci. USA* 95:11083-11088, 1998, hereafter "Miyamoto), both of record. Applicants traverse the rejection, which is improper. Both of the cited references were of record in earlier information disclosure statements that applicants filed. The Office considered both of the references, as shown by the signed and initialed information disclosure statements in the image file wrapper for this application. There is no reason that the Office could not have issued this rejection earlier. This piecemeal prosecution needlessly increases the cost for Applicants to prosecute this application and needlessly drags the prosecution out.

Piecemeal prosecution is dealt with at MPEP § 707.07(g) as follows: "Piecemeal examination should be avoided as much as possible. The examiner ordinarily should reject each claim on all valid grounds available, avoiding, however, undue multiplication of references." Applicants have paid all of their fees in good faith and to have to address this rejection now is simply unreasonable. Applicants note that no claim amendment in their prior response necessitated this rejection. Applicants request withdrawal of the finality of the rejection in view of this new ground of rejection over references that were of record earlier in the prosecution of this case. Applicants urgently request immediate cessation of this improper prosecution tactic.

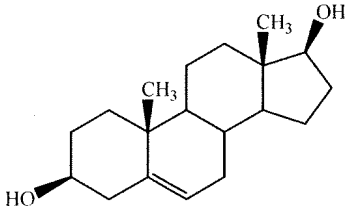
In addition to the improper piecemeal nature of the rejection, Applicants respectfully submit that the cited references, either alone or together, do not

render the present claims obvious. The courts have discussed obviousness which guides the analysis, e.g., *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966); *KSR Int'l v. Teleflex, Inc.*, 550 U.S. ___ (2007). For chemical compounds, comparison of claimed chemical structures and prior art structures is usually a component of the analysis, e.g., *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990) (in banc), cert. denied, U.S. , 111 S. Ct. 1682 (1991); *Yamanouchi Pharmaceutical Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 56 USPQ2d 1641 (Fed. Cir. 2000); *In re Deuel*, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995); *In re May*, 574 F.2d 1082 (C.C.P.A. 1978); *In re Wilder*, 563 F.2d 457, (C.C.P.A. 1977); *In re Hoch*, 428 F.2d 1341 (C.C.P.A. 1970). The court has also stated that "generalization is to be avoided insofar as specific structures are alleged to be *prima facie* obvious one from the other." *In re Jones*, 958 F.2d 347; 21 U.S.P.Q.2D 1941 (Fed. Cir. 1992), citing *In re Grabiak*, 769 F.2d 729, 731, 226 USPQ 870, 872 (Fed. Cir. 1985). Thus, a species claim is "not necessarily obvious in light of a prior art disclosure of a genus." *Eli Lilly & Co. v. Barr Lab., Inc.* 222 F.3d 973; 55 USPQ2D 1609 (Fed. Cir. 2000), citing *In re Baird*, 16 F.3d 380, 29 U.S.P.Q.2D 1550 (Fed. Cir. 1994). The use of hindsight to construct an obviousness rejection is also impermissible. *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999); *KSR Int'l v. Teleflex, Inc.*, 550 U.S. ___ (2007).

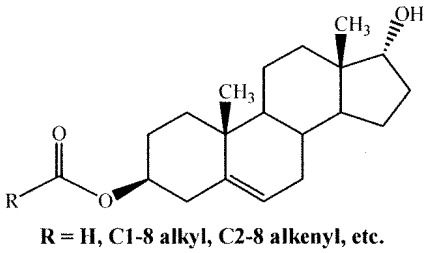
The Miyamoto article describes the phenomenon of androgen receptor activation by androst-5-ene-3β,17β-diol (referred to as "Adiol" in Miyamoto), an observation that was apparently not previously reported. The Miyamoto reference stated that the antiandrogens hydroxyflutamide and casodex (both are nonsteroid antiandrogens) did not antagonize the capacity of androst-5-ene-3β,17β-diol to increase androgen receptor transcriptional activity. The WO 97/37662 publication described the effect of androst-5-ene-3β,17α-diol on proliferation of ZR-75-1 cells *in vitro*. The presently claimed compounds differ structurally from the compounds that Miyamoto and WO 97/37662 describe and they are thus not obvious over either reference alone or together. In particular, the amended claims require a methylcarbonate moiety (-O-C(O)-OCH_3) for the R^5 variable at the 3-position and

an ethynyl (-CCH) or propynyl (-$CCCH_3$) moiety for the R^{19} variable at the 17-position. Neither Miyamoto nor WO 97/37662 disclose either of these substituents and these references therefore do not constitute a *prima facie* case of obviousness for the amended claims.

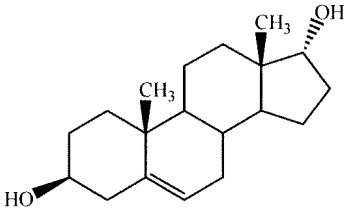
Representative structures are shown below to assist the Office's review of the differences between the claimed subject matter and compounds described in the cited references.



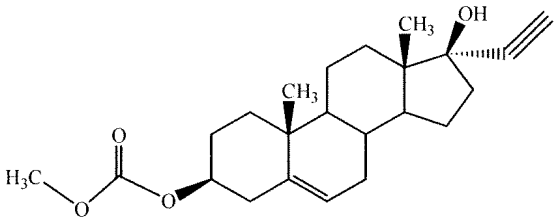
Adiol
androst-5-ene-3β,17β-diol
Miyamoto



androst-5-ene-3β,17α-diol
3β-ester
WO 97/37662



androst-5-ene-3β,17α-diol
WO 97/37662



17α-ethynylandrost-5-ene-3β-methyl carbonate-17β-ol
Claim 85

At page 8 of the office action, the Office stated: "Miyamoto et al disclose that Adiol can activate androgen receptor (AR) target genes in human prostate cancer cells. Therefore a person having ordinary skill in the art at the time the claimed invention was made would have been motivated to use Adiol to treat prostate cancer." Applicants respectfully traverse the Office's conclusion, which is incorrect. The Office has clearly misunderstood what Miyamoto described and therefore misapplied Miyamoto in casting the rejection.

Miyamoto suggested that activation of androgen receptor by Adiol could be a reason that androgen antagonists ultimately fail in prostate cancer treatment protocols. Miyamoto suggested that Adiol itself was an endogenous androgen

that could cause androgen blockade to fail and progression or worsening of prostate cancer. Clearly, a person having ordinary skill in the art at the time the claimed invention was made would have known that Adiol should not be used to treat prostate cancer because the androgen activity of Adiol itself could cause the disease to progress. The Miyamoto publication showed that two potent nonsteroidal antiandrogens, hydroxyflutamide and bicalutamide, both failed to inhibit the capacity of Adiol to activate the androgen receptor. The failure of nonsteroidal antiandrogens to antagonize the activity of Adiol thus provided no basis for one of ordinary skill in the art to select any particular chemical structure that could antagonize this aspect of Adiol biological activity. In casting the rejection, the Office identified no structure in Miyamoto that would lead to the presently claimed chemical structures. If the rejection is based on a hindsight analysis, it must be withdrawn. *In re Dembiczak*, above; *KSR Int'l v. Teleflex, Inc.*, above.

Because the Office has misunderstood the meaning and content of Miyamoto, the Office's reasoning to establish the rejection is in error and it must be withdrawn. Such reasoning cannot properly be used to establish a *prima facie* case of obviousness. A showing of obviousness under 35 USC § 103(a) requires a correct understanding and application of any cited reference. Absent that, there would be no rational basis for an obviousness rejection.

In view of the claim amendments and the foregoing arguments, Applicants respectfully request reconsideration and withdrawal of the rejection.

Consideration of cited publications

The Office alleged that Applicants failed to comply with the requirements of 1.98(a)(2) with the information disclosure statement (IDS) submitted with their response of February 22, 2007. Applicants respectfully traverse the Office's allegation and they request consideration of the cited references, which is proper under the circumstances described below.

MPEP § 609.05(c) states:

> "[t]o the extent that a document is submitted as evidence directed to an issue of patentability raised in an Office action, and the evidence is timely presented, applicant need not satisfy the requirements of 37 CFR 1.97 and 37 CFR 1.98 in order to have the examiner consider the information contained in the document relied on by applicant. In other words, compliance with the information disclosure rules is not a threshold requirement to have information considered when submitted by applicant to support an argument being made in a reply to an Office action."

The cited references were submitted as evidence directed to an issue of patentability raised in an Office action and they therefore should have been considered under the provisions of MPEP § 609.05(c).

The listed documents were submitted as shown by the electronic acknowledgement receipt generated from the EFS-Web submission in the February 22, 2007 status letter to Applicants in the image file wrapper. It should be noted that "[t]he acknowledgment receipt contains the 'receipt date,' the time the correspondence was received at the Office and a full listing of the correspondence submitted. Accordingly, an acknowledgment receipt is a legal equivalent of a post card receipt described in the Manual of Patent Examining Procedure (MPEP), Section 503" (Federal Registry Vol. 72, No. 14, p. 2770 January 23, 2007). The non-patent literature documents at issue are identified in the February 22, 2007 electronic acknowledgement receipt by last name of the first author of the document that is present in the file name of the PDF that was attached to the e-filed IDS.

The rules for receipt of papers by EFS are governed by the EFS-Web Legal Framework, which state "*[t]o the extent that any USPTO regulation is inconsistent with EFS, the regulation will be interpreted in a manner to support EFS and waived, when necessary, until formal regulations directed to electronic submissions are promulgated* (Emphasis in original)". The EFS legal framework thus controls and the references should properly have been considered.

In view of the foregoing, Applicants request consideration of the references they cited in the prior IDS.

Withdrawal of 102(a) Rejection Previously Imposed

In the previous Office action, the Office imposed a 102(a and f), or in the alternative 103(a), rejection in view of Chang, et al (*Proc. Natl. Acad. Sci. USA* Vol. 96, Issue 20, 11173-11177, September 28, 1999). To overcome these rejections, Applicants submitted an affidavit under 37 CFR §1.131 establishing their prior inventorship of the claimed subject matter. In the Final Office action, the Office is silent on this point. Applicants therefore respectfully request notification of the withdrawal of this §102 rejection in the Office's next communication.

Date: June 5, 2007

Respectfully submitted,
/ Daryl D. Muenchau /

Daryl D. Muenchau
Reg. No. 36,616
Hollis-Eden Pharmaceuticals, Inc.
4435 Eastgate Mall, Suite 400
San Diego, CA 92121
Phone: 858-587-9333 x439
Fax: 858-558-6470